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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Persistence on anti-TNF therapy – data from Serbian National Spondyloarthritis Registry

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SUMMARY

Introduction/Objective The aim of our study was to retrospectively analyze data about efficacy and persistence on different anti-TNFα treatment in spondyloarthritis (SpA).

Methods We retrospectively analyzed SpA patients whose data were entered into the Serbian national SpA registry. All patients were divided in two groups: non-switcher (patients who were treated with one anti-TNFα) and switcher group (who has switched from first to second and third anti-TNFα). Disease activity was measured by the Ankylosing Spondylitis Disease Score and the Bath Ankylosing Spondylitis Disease Activity Index and functional status was measured by the Bath Ankylosing Spondylitis Functional Index.

Results We identified 290 SpA patients – 250 patients with axial SpA (axSpA) and 40 patients with peripheral SpA (pSpA). Among 250 patients with axSpA, 192 (76.8%) did not change first anti-TNFα, while 58 (23.2%) switched to the second and 14 (5.6%) switched to the third anti-TNFα. Among 40 patients with pSpA, 29 (72.5%) did not change first anti-TNFα while 11 (27.5%) switched to the second and three (7.5%) switched to the third anti-TNFα. Survival on the first anti-TNFα was 35.16 ± 28.5 months (switchers 29.41 ± 21.89 *vs.* non-switchers 36.89 ± 30.04). At the moment of this cross-section 37 (19.3%) patients still had very high disease activity, while only 75 (39%) patients had inactive disease.

Conclusions In real-life clinical practice in our country, as well as in others, there is reluctance to anti-TNFα switch in SpA patients. Administrative limitations and national reimbursement policy could be one of the main reasons limiting treat to target implementation in SpA patients. Additionally, specific drug efficacy on extra-articular manifestations is often the reason for choosing the first line medication or switching to the next one.

Keywords: anti-TNFα drugs; anti-TNFα switch; registry; spondyloarthritis

INTRODUCTION

Spondyloarthritis (SpA) is a heterogeneous group of chronic inflammatory joint diseases. Depending on the clinical presentation and joint involvement, SpA is divided into axial (axSpA) and peripheral (pSpA) form of the disease. The clinical manifestations of SpA include arthritis, dactylitis, enthesitis, and typical extra-articular manifestations (EAM), such as psoriasis, acute anterior uveitis, and inflammatory bowel disease (IBD) [1]. In the last decades, due to the usage of biological drugs such as TNF-α inhibitors, there were great achievements in the treatment in terms of reduction of the disease activity, improvement of functional capacity and the quality of life of these patients. All TNF-α inhibitors (infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol) are effective in treating different forms of SpA, but it is also known that some patients do not respond to treatment at the very beginning of the therapy or stop responding to the medication over time due to secondary ineffectiveness or adverse effects of the drug [2].

There are also differences in the efficacy of different anti-TNFα agents in relation to the presence of EAM and this should be included when choosing treatment option [3]. For example, in acute anterior uveitis adalimumab and infliximab showed better treatment results than treatment with etanercept [4]. Etanercept is ineffective in IBD [5] and some data suggest that it may also be less effective than adalimumab in patients with psoriasis [6]. Among the TNFα-blocking agents, only infliximab and adalimumab are effective in SpA and IBD [7, 8].

As TNF-α inhibitors are different in structure and mechanism of action, patients who fail to respond to treatment with first anti TNFα drug or receive some adverse reactions during therapy, may benefit from the application of the second anti TNFα drug [9].

The aim of our study was to retrospectively analyze everyday practice data about efficacy and persistence on different anti TNF treatment in SpA patients followed up as observational cohort within the National Biologics' Registry and in accordance with medication evaluability.

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METHODS

We have retrospectively analyzed data of SpA patients who were entered into the Serbian national SpA registry (2009–2018). The Serbian National Biologics Registry is official software application established and founded by the Serbian Rheumatology Association after obtaining IRB/EC approval. It is based on Declaration of Helsinki and other relevant regulations to protect patient privacy. Registry enables all rheumatologists across the country to enter patient data during regular periodic follow up classified in four domains: basic demographic data, disease onset and history, outcome measures (disease activity) and safety data. Data entry started in 2009 when biologics became evaluable and reimbursed by National Health Insurance Fund (NHIF). The first evaluable biologic was etanercept (in 2009) followed by adalimumab in 2011 and golimumab in 2015. Secukinumab, as IL-17 blocker, become evaluable at the end of 2019 while other biologics are yet not present.

SpA diagnosis was established using Modified New York criteria [10] for patients who started treatment from 2009 up to 2013 or using the Assessment of Spondyloarthritis International Society (ASAS) criteria for patients who started treatment after 2013 [11]. All patients fulfilled ASAS classification criteria for diagnosis of axial or peripheral SpA [11]. Patients with psoriasis and SpA disease features were classified as psoriatic arthritis and were not included in this study. Only patients who had details about the disease diagnosis, activity, treatment and follow up data at the moment of this cross-sectional analysis were eligible for inclusion into the study. Disease activity was measured by the Ankylosing Spondylitis Disease Score (ASDAS) and/or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and functional status was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI). Radiographically confirmed sacroiliitis was defined as bilateral grade II/IV or unilateral grade III/IV sacroiliitis according to New York criteria [10] in patients enrolled before 2013 while magnetic resonance imaging was used for patients enrolled later on. For patients enrolled before 2013, according to data entered into the system in the past, ASDAS score was calculated retrospectively and used for analysis.

Data collected and analyzed were sex, age, disease duration before starting biologic therapy, the length of treatment with each anti-TNFα, presence of different EAM, drug persistence, reasons for drug discontinuation and switch to next anti-TNFα and side effects recorded during follow up. According to treatment used all patients were divided in two groups: non-switcher (including patients who were treated with only one anti-TNFα as a first biologic drug) and switcher group (including patients who switched from first to second and third anti-TNFα). According to the axSpa national treatment algorithm [12] and NHIF regulation, patients who had high disease activity (BASDAI ≥ 4, and ASDAS C-reactive protein values ≥ 2.1) after applying the previous treatment modality (non-steroidal anti-rheumatic drugs in axSpA and chemical disease modifying drugs and local corticosteroids in pSpA, were approved to, start treatment with biological drugs (bDMARDs).

All bDMARDs were used according to their summary of product characteristic and standard clinical practice. When patients fail to respond to treatment after six months, they should be switched from the first to the second and some of them with the same reason to the third anti-TNFα drug.

Lack of reduction in BASDAI index by 50% or ≥ 2 of pre-drug value, or no decrease in ASDAS index ≥ 1.1 in the first six months of treatment was defined as primary inefficacy, while insufficient reduction in BASDAI or ASDAS score after at least 12 months of treatment with primary good response to the drug, was defined as secondary treatment inefficacy.

Drug survival was calculated as the number of months from first to last dose of the same drug at the time of the cross-section. The efficacy of the biological drug as the first, second or third line was measured as a change of the BASDAI and/or ASDAS score from the initial dose of the specific medication.

Statistical methods

Differences in average age at diagnosis, age at initiation of therapy, duration of disease until initiation of therapy between switchers and non-switchers, were tested by t-test. Previously, the normality of the observed values was confirmed by the Kolmogorov–Smirnov test. Differences in the length of drug administration as the first drug were tested by ANOVA. Differences in the presence of EAM between switchers and non-switchers and the association between the first drug and presence of EAM were tested by χ^2 test.

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008 (5), as well as the national law. All the data were retrospectively analyzed from Serbian National Registry for Spondyloarthritis formed with the approval of the Ethics Committee of the Institute of Rheumatology in Belgrade. Code availability: not applicable.

RESULTS

We have identified a total of 290 SpA patients who fulfilled inclusion criteria regarding the availability of data entered into the registry. There were 250 patients with axSpA and 40 patients with pSpA. Detailed demographic characteristics are presented in Table 1.

Patients with axial spondyloarthritis

Among 250 patients with axial SpA, 192 (76.8%) did not change first anti-TNFα (non-switcher group), while 58 (23.2%) switched to the second anti-TNFα and 14 (5.6%) switched to the third anti-TNFα (switcher group).

Patients in non-switcher group had significantly shorter disease duration before introduction of biologic therapy (Table 1). In the same group of patients there

Table 1. Demographic characteristics for axial spondyloarthritis and peripheral spondyloarthritis patients

Parameters	All	Axial spondyloarthritis			Peripheral spondyloarthritis		
	n = 250	non-switchers (n = 192)	switchers (n = 58)	t	non-switchers (n = 29)	switchers (n = 11)	t
		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Age at diagnosis (years)	32.89 ± 11.32	32.81 ± 11.20	34.09 ± 11.53	2.54	32.25 ± 12.85	25.09 ± 10.87	-5.59
Disease duration (years)	10.2 ± 8.2	9.20 ± 7.48	13.48 ± 9.54	10.09**	7.18 ± 6.18	14.64 ± 9.19	7.70*
Disease duration before biologic therapy (years)	6.23 ± 7.47	5.59 ± 7.06	8.33 ± 8.40	6.71*	4.98 ± 6.29	9.27 ± 7.47	4.56
Treatment duration of biologic therapy (months)	41.3 ± 31.57	36.90 ± 30.03	55.88 ± 32.38	22.36**	26.04 ± 20.31	64.73 ± 26.94	22.48**
Clinical manifestations							
		n (%)	n (%)	χ^2	n (%)	n (%)	χ^2
Radiographically confirmed sacroiliitis	214	169 (88.02)	45 (77.59)	3.93*	19 (65.52)	3 (27.27)	5.29*
Peripheral arthritis	101	78 (40.63)	23 (29.66)	0.02	28 (96.55)	10 (90.91)	0.54
Dactylitis	10	10 (5.21)	0 (0)	3.14	5 (17.24)	1 (9.09)	0.42
Enthesitis	54	41 (21.35)	13 (22.41)	0.03	20 (68.97)	7 (63.64)	0.10
Iridocyclitis/uveitis	48	39 (20.31)	9 (15.52)	0.99	4 (13.79)	2 (18.18)	0.12
Inflammatory bowel disease (Crohn's disease / ulcerative colitis)	15	6 (3.31)	9 (15.52)	12.08**	3 (10.34)	2 (18.18)	0.45

Data shown in the upper part of the table (continuous variables) represent mean ± SD; data shown in the lower part of the table are frequencies (counts) of patients with particular articular and extra-articular manifestations
* $p < 0.05$;
** $p < 0.01$

Table 2. Articular and extra-articular manifestations of axial spondyloarthritis patients at the time of anti-TNF introduction in switchers and non-switchers group

Parameters	Non-switchers					Switchers				
Anti TNF used	Adalimumab (n = 64)	Etanercept (n = 64)	Golimumab (n = 57)	Infliximab (n = 7)	χ^2	Adalimumab (n = 15)	Etanercept (n = 27)	Golimumab (n = 9)	Infliximab (n = 7)	χ^2
Radiographically confirmed sacroiliitis	55 (85.94%)	53 (82.81%)	56 (98.25%)	5 (71.43%)	9.39*	12 (80%)	19 (70.37%)	8 (88.89%)	6 (85.71%)	1.78
Peripheral arthritis	31 (48.44%)	28 (43.75%)	17 (29.82%)	2 (28.57%)	5.06	6 (40%)	9 (33.33%)	4 (44.44%)	4 (57.14%)	1.43
Dactylitis	6 (9.38%)	1 (1.56%)	3 (5.26%)	0 (0%)	4.36	0 (0%)	0 (0%)	0 (0%)	0 (0%)	/
Enthesitis	12 (18.75%)	13 (20.31%)	14 (24.56%)	2 (28.57%)	0.87	5 (33.33%)	5 (18.52%)	2 (22.22%)	1 (14.29%)	1.53
Iridocyclitis/ uveitis	26 (40.63%)	5 (7.81%)	8 (14.04%)	1 (14.29%)	26.85**	4 (26.67%)	3 (11.11%)	0 (0%)	2 (28.57%)	4.38
Inflammatory bowel disease (Crohn's disease/ ulcerative colitis)	3 (4.69%)	1 (1.56%)	1 (1.75%)	1 (14.29%)	4.15	4 (26.67%)	2 (7.41%)	0 (0%)	3 (42.86%)	8.12*

* $p < 0.05$;
** $p < 0.01$

were significantly more patients with radiographically confirmed sacroiliitis ($p < 0.05$), and statistically less patients with IBD compared to switchers group ($p < 0.001$) (Table 1).

Median survival of the first TNF alpha inhibitors in all axSpA patients was 35.16 ± 28.5 months (switchers 29.41 ± 21.89 *vs.* non-switchers 36.89 ± 30.04). In non-switchers group etanercept was the most commonly used anti-TNFα as the first drug compared to other TNFα inhibitors ($p < 0.001$). In the non-switchers group, patients with iridocyclitis were more frequently treated with adalimumab as the first drug ($p < 0.001$), while in those without eye manifestation etanercept or golimumab were the first drug (Table 2).

Out of 192 patients with axSpA in non-switchers group at the beginning of the treatment, 135 had a very high disease activity (VHDA) according to the ASDAS score. At the moment of this cross-section, 30 (15.6%) patients were still having VHDA, seven (3.7%) had high disease activity (HAD), 80 (41.7%) minimal disease activity (MDA), and 75 (39%) patients had inactive disease (ID). The details are presented in Figure 1. The second anti-TNFα drug survival for switchers was 22.14 ± 20.29 months and for the third-time anti-TNFα switchers it was 26.57 ± 35.8 months. In the same group etanercept was the most common drug to be changed (29; 50%), while adalimumab was most commonly used as the second anti-TNFα (23; 39.7%) and golimumab as the third anti-TNF α (8; 57.1%).

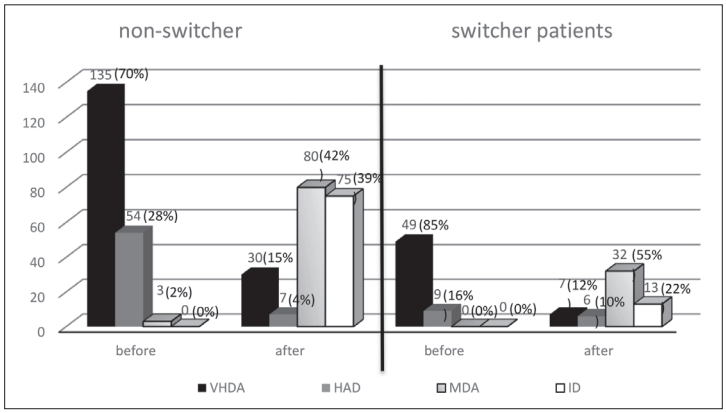

Figure 1. Disease activity at the beginning and at time of cross-section in non-switchers and switcher group patients with axial spondylarthritis; VHDA – very high disease activity; HAD – high disease activity; MDA – minimal disease activity; ID – inactive disease

After the treatment with the third TNFα inhibitor, two patients still had VHDA (both patients were receiving drug less than six months), four patients had HDA (two patients were receiving drug less than six months), while five patients had MDA and three patients ID. At the time of cross-section in whole switchers group, among 58 patients, 13 patients (22.4%) had ID, 32 (55.2%) MDA, six (10.3%) had HDA and seven (12.1%) VHDA (Figure 1).

All indices (BASDAI, BASFI, and ASDAS) were statistically significantly lower at cross-sectional time point compared to the initiation period of the treatment in patients with axSpA (Table 3).

The reasons for switching or discontinuing TNFα blockers were:

1. inadequate response to drug (insufficient reduction in ASDAS score or BASDAI index);
2. side effect of the drug;
3. development of extra-articular manifestation;
4. on patient's request (e.g., planned pregnancy, disease remission).

Reasons for switching from the first anti-TNFα include secondary inefficiency in 40 (68.97%), primary inefficiency in six patients (10.34%), recurrent uveitis and IBD each in one patient (1.72%), and elevated transaminases in one (1.72%) patient. Nine patients stopped treatment due to remission (five patients, 8.6%) and administrative reasons (four patients, 6.9%).

Reasons for switching from the second anti-TNFα were: secondary inefficiency in six (42.86%), primary inefficiency in four (28.57%), remission of Crohn's disease in one (7.14%), pregnancy in one (7.14%) and skin changes in two patients (14.29%).

In the switchers group (n = 58), at the beginning of the treatment with the second anti TNFα drug, 49 patients had VHDA and nine had HAD, while at the moment of cross-section only 10 patients had ID after treatment with the second anti TNFα drug. In the group of VHDA and HDA there were seven patients who had started biologic therapy six months or less before the cross-section moment, while 14 patients from this group switched to the third TNFα inhibitor.

Patients with peripheral SpA

Among 40 patients with pSpA, 29 (72.5%) did not change first anti-TNFα (non-switchers) while 11 (27.5%) switched to the second anti-TNFα and three (7.5%) switched to the third anti-TNFα (switchers).

Patients in non-switchers group had significantly shorter duration of the disease in general and before starting biologic therapy (Table 1).

A total of 38 patients were under concomitant therapy with DMARD – 12 patients on methotrexate at an average dose of 13.44 ± 5.5 mg, 19 patients on sulfasalazine and seven patients on methotrexate and sulfasalazine.

Survival on the first TNFα inhibitor in all pSpA patients was 27.4 ± 22.35 months (in switchers 27.4 ± 22.35, and in non-switchers 25.2 ± 21.4), on the second drug 28.64 ± 14.1 months, and on the third it was 16.33 ± 7.37 months. In pSpa non-switchers, most commonly used first anti-TNFα was adalimumab (12 patients; 41.4%), while etanercept was used in nine (31%), golimumab was in six patients (20.7%) and infliximab in two (6.9%) patients. In pSpA switchers adalimumab was most commonly used as the first drug, but it was also the most often changed drug in these patients. As in the axSpA switchers, golimumab was most commonly used as the third drug (in all three patients).

In pSpA switchers and non-switchers group there was no significant difference in the use of any of the TNFα inhibitors as the first drug, compared to the presence of articular and EAM.

Table 3. The value of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Ankylosing Spondylitis Disease Score (ASDAS) indexes before first anti-TNF drug and at cross-sectional time in axial spondyloarthritis patients (n = 250)

Index	Before TNFα inhibitor in non-switchers	Actual in non-switchers	t	Before the first TNFα inhibitor in switchers	Before the second TNFα inhibitor in switchers	t	Before the third TNFα inhibitor in switchers	Actual in switchers	t
BASDAI	6.1 ± 1.59	2.07 ± 1.57	29.35**	6.2 ± 1.61	5.48 ± 1.68	3.68	5.65 ± 0.91	2.5 ± 1.53	7.36**
BASFI	5.6 ± 1.78	2.08 ± 1.93	22.07**	6.42 ± 1.65	5.6 ± 1.68	4.16	4.72 ± 2.25	2.38 ± 2.15	3.94**
ASDAS	4.05 ± 0.98	1.56 ± 0.98	29.48**	4.44 ± 0.96	3.87 ± 0.75	5.09	3.59 ± 0.67	2.08 ± 1.0	4.11**

Data shown in the upper part of the table represent mean ± SD; significances presented by asterisks are significances of t-test comparing means of indices of non-switchers and switchers between different stages of medical treatment;
**p < 0.001

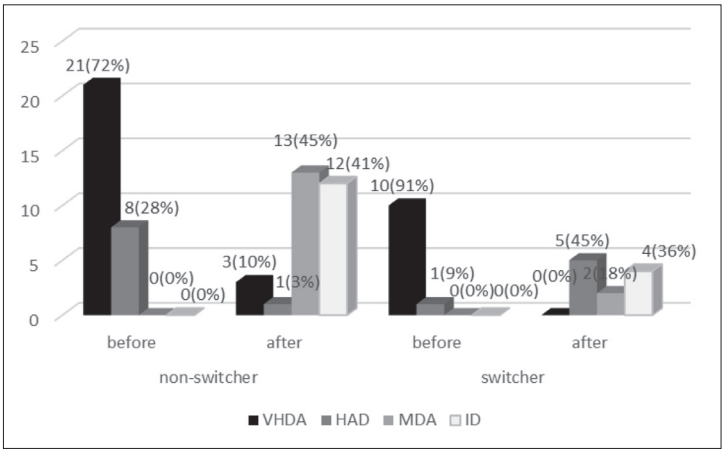

Figure 2. Disease activity at the beginning and at time of cross-section in non-switchers and switcher group patients with peripheral spondylarthritis; VHDA – very high disease activity; HAD – high disease activity; MDA – minimal disease activity; ID – inactive disease

Reasons for switching the first drug were: secondary inefficiency in six (54.55%), primary inefficiency, recurring iridocyclitis and administrative reasons, each in one patient (9.09%), and remission in two patients (18.18%). Reason for switching the second drug in all three patients was secondary inefficiency.

At the beginning of the treatment in non-switchers group 21 patients had VHDA according to the ASDAS score and 8 had HDA. At the moment of intersection three (10.4%) patients were in the group of VHAD and one patient (3.4%) in HAD, 13 had (44.8%) MDA and 12 had (41.4%) ID. In the group of VHDA and HDA there were two patients who had started biologic therapy six months or less before the moment of intersection.

After the treatment with the second TNFα inhibitor, three patients still presented VHDA and two patients had HDA (these two patients were treated by second drug less than six months at the time of intersection), two patients had MDA and four patients had ID. All three patients from the group of VHDA were switched to the third TNFα inhibitor. Out of these three patients, two patients still had HDA, and one patient had MDA. In whole switchers group at the time of intersection five (45.4%) patients had HAD, two had (18.2%) MDA and four had (36.4%) ID (Figure 2).

In the whole group of pSpA patients the value of index ASDAS was statistically significantly lower at cross-sectional time point compared to the onset of treatment in switchers (4.05 ± 0.75 *vs.* 1.71 ± 0.73) and in non-switchers (4.07 ± 0.95 *vs.* 1.58 ± 1.08, $p < 0.001$).

DISCUSSION

Our study analyzed real practice data and found out that one third of patients with axSpA (23.2%) and pSpA (27.5%) switched to second TNFα inhibitor and only a small number of them switched to the third anti TNFα drug during a follow-up period of nine years. These results are in accordance with French registries, where switching rate for the first anti TNF alpha drug was of 32% in patients with spondyloarthropathy [13, 14]. In the Norwegian-NOR-DMARD registry only 14.9% of AS patients switched the first anti TNF alpha drug during in a period of nine years [15]. Also, in the Danish-DANBIO registry 30% of patients had switched once and 10% patients had switched twice during a 10-year-long follow-up [16].

Disease duration in non-switcher group of patients with axSpA and pSpA, as might be expected, was significantly shorter compared to switcher group. Many studies have proved that initiation of anti-TNFα drug in the earlier course of the disease reduces the inflammation at earlier stage and provides better chance for favorable outcome [17]. Accordingly, non-switcher axSpA patients were younger at the time of biologic therapy commencement compared to switchers group. This is not in line with the findings of other national registers where shorter disease and symptom duration and higher disease activity and functional indices were found in switchers compared to non-switchers [15, 16].

We assume this is a direct consequence of difference in anti-TNF therapy availability in each country. Unfortunately, anti-TNFα biologics became treatment option for these patients rather late in Serbia (etanercept in 2009, adalimumab and infliximab in 2011, golimumab in 2015). This fact probably explains why etanercept was found to have the longest persistence rate in all SpA patients, compared to other anti TNFα drugs, while it was also found to be the most often changed first anti-TNFα medication, as recorded in our study.

The most common reasons for switching etanercept as first line anti-TNFα in axSpA group of patients were secondary inefficacy and the presence of extraarticular manifestations, such as IBD and recurrent uveitis. In these patients, according to its proven efficacy [18], adalimumab was the second anti-TNFα chosen. Probably due to the same reason, adalimumab was the preferable first anti-TNF for patients in the non-switcher group with a history of uveitis revealed by anamnestic data, while in the switchers axSpA group of patients the presence of IBD was the reason for switching to adalimumab or infliximab. So, similar to other registries and according to official recommendations [19], the presence of EAM influence the choice and persistence of first anti-TNF.

It is interesting that in pSpA patients the most commonly used first anti-TNFα was adalimumab, while this group of patients often had EAM. Golimumab was the most often used as the third TNFα inhibitor in axSpA and pSpA switchers, because it was the last anti-TNFα drug introduced on Serbian pharmaceutical market. It was mostly used in patients who have developed secondary inefficiency or side effects after treatment with etanercept, adalimumab, or infliximab.

Like in previous studies, the most common reason for drug switching was secondary inefficiency in our study as well [15]. Survival time on the second and third

medication was shorter compared to initial therapy both in the pSpA and in the axSpA which suggests that the risk of switching is higher over time.

The results of our study showed that two thirds of patients with axSpA (75.86%) and pSpA (72.73%) who switched the first TNFα inhibitor were responsive to the second drug which is consistent with the available data in the literature [20]. But there were still axSpA and pSpA patients who, despite switching to the third drug, could not reach the therapeutic goal. Here it is necessary to rise question of outcome measures used to assess disease outcome and activity. Until 2013 in our country BASDAI index was used to assess disease activity and after that period we started to use ASDAS index. Given that the calculation of BASDAI index is based on a subjective assessment of the patient's discomfort, we can say that this previously used measure of disease activity was less sensitive compared to the composite ASDAS index, which includes clinical and laboratory parameters. It is assumed that earlier use of the ASDAS index would provide better insight into disease activity and, if necessary, earlier and more effective changing of the biological drug [21]. At the same time, we can say that this is the main limitation of our study. Another limitation of this study is the small number of patients who are treated with biologics in this indication in our country – for economic reasons. The interleukin 17 inhibitor was approved in our country in this indication in 2019, so that is why we did not consider switching TNF alpha inhibitors to this drug.

CONCLUSIONS

In real-life clinical practice in our country, as well as in others, there is reluctance to anti-TNFα switch in SpA patients. Administrative limitations and national reimbursement policy (late initiation of treatment and late switching to another drug) could be one of the main reasons limiting treat to target implementation in SpA patients, which may explain the still high disease activity in some of our patients. Additionally, specific drug efficacy on EAM is often the reason for choosing the first line medication or switching to the next one.

Conflict of interest: None declared.

REFERENCES

1. Sharip A, Kunz J. Understanding the Pathogenesis of Spondyloarthritis. Biomolecules. 2020;10(10):1461. [DOI: 10.3390/biom10101461] [PMID: 33092023]
2. Toussirot E. Pharmacological management of axial spondyloarthritis in adults. Expert Opin Pharmacother. 2019;20(12):1483–91. [DOI: 10.1080/14656566.2019.1617853] [PMID: 31095430]
3. van der Meer R, Arends S, Kruidhof S, Bos R, Bootsma H, Wink F, et al. Extraskeletal Manifestations in Axial Spondyloarthritis Are Associated With Worse Clinical Outcomes Despite the Use of Tumor Necrosis Factor Inhibitor Therapy. J Rheumatol. 2022;49(2):157–64. [DOI: 10.3899/jrheum.210308] [PMID: 34393101]
4. Lee S, Park YJ, Lee JY. The Effect of Tumor Necrosis Factor-Alpha Inhibitors on Uveitis in Patients with Ankylosing Spondylitis. J Korean Med Sci. 2019;34(42):e278. [DOI: 10.3346/jkms.2019.34.e278] [PMID: 31674159]
5. Korzenik J, Larsen MD, Nielsen J, Kjeldsen J, Nørgård BM. Increased risk of developing Crohn's disease or ulcerative colitis in 17 018 patients while under treatment with anti-TNFα agents, particularly etanercept, for autoimmune diseases other than inflammatory bowel disease. Aliment Pharmacol Ther. 2019;50(3):289–94. [DOI: 10.1111/apt.15370] [PMID: 31267570]
6. Zweegers J, Groenewoud JMM, van den Reek JMPA, Otero ME, van de Kerkhof PCM, Driessen RJB, et al. Comparison of the 1- and 5-year effectiveness of adalimumab, etanercept and ustekinumab in patients with psoriasis in daily clinical practice: results from the prospective BioCAPTURE registry. Br J Dermatol. 2017;176(4):1001–9. [DOI: 10.1111/bjd.15023] [PMID: 27579864]
7. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Safdi M, Popp JW Jr, et al. Infliximab for Crohn's Disease: More Than 13 Years of Real-world Experience. Inflamm Bowel Dis. 2018;24(3):490–501. [DOI: 10.1093/ibd/izx072] [PMID: 29462395]
8. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018;113(4):481–517. [DOI: 10.1038/ajg.2018.27] [PMID: 29610508]
9. Manica SR, Sepriano A, Pimentel-Santos F, Gouveia N, Barcelos A, Branco JC, et al. Effectiveness of switching between TNF inhibitors in patients with axial spondyloarthritis: is the reason to switch relevant? Arthritis Res Ther. 2020;22(1):195. [DOI: 10.1186/s13075-020-02288-8] [PMID: 32825839]
10. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27(4):361–8. [DOI: 10.1002/art.1780270401] [PMID: 6231933]
11. Rudwaleit M, van der Heijde D, Landewé R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of Spondyloarthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011;70(1):25–31. [DOI: 10.1136/ard.2010.133645] [PMID: 21109520]
12. van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017;76(6):978–91. [DOI: 10.1136/annrheumdis-2016-210770] [PMID: 28087505]
13. Krajewski F, Andras L, Pereira-Gillion C, Goupille P, Salliot C. Drug maintenance of a second tumor necrosis factor alpha inhibitor in spondyloarthritis patients: A real-life multicenter study. Joint Bone Spine. 2019;86(6):761–7. [DOI: 10.1016/j.jbspin.2019.07.003] [PMID: 31326602]
14. Paccou J, Solau-Gervais E, Houvenagel E, Salleron J, Luraschi H, Philippe P, et al. Efficacy in current practice of switching between anti-tumour necrosis factor- α agents in spondyloarthropathies. Rheumatology (Oxford). 2011;50(4):714–20. [DOI: 10.1093/rheumatology/keq377] [PMID: 21131271]
15. Lie E, van der Heijde D, Uhlig T, Mikkelsen K, Rødevand E, Koldingsnes W, et al. Effectiveness of switching between TNF inhibitors in ankylosing spondylitis: data from the NOR-DMARD register. Ann Rheum Dis. 2011;70(1):157–63. [DOI: 10.1136/ard.2010.131797] [PMID: 21062852]
16. Glintborg B, Østergaard M, Krogh NS, Tarp U, Manilo N, Loft AG, et al. Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumor necrosis factor α inhibitor therapy: results from the Danish nationwide DANBIO registry. Ann Rheum Dis. 2013;72(7):1149–55. [DOI: 10.1136/annrheumdis-2012-201933] [PMID: 22941767]
17. Nam EJ, Lee WK. Early Improvements in Disease Activity Indices Predict Long-Term Clinical Remission Suggested by the Treat-to-Target Strategy in Patients with Ankylosing Spondylitis Receiving TNF-α Inhibitor Treatment. J Clin Med. 2021;10(18):4279. [DOI: 10.3390/jcm10184279] [PMID: 34575390]
18. Lee S, Park YJ, Lee JY. The Effect of Tumor Necrosis Factor-Alpha Inhibitors on Uveitis in Patients with Ankylosing Spondylitis. J Korean Med Sci. 2019;34(42):e278. [DOI: 10.3346/jkms.2019.34.e278] [PMID: 31674159]

19. Lindström U, Olofsson T, Wedrén S, Qirjazo I, Askling J. Impact of extra-articular spondyloarthritis manifestations and comorbidities on drug retention of a first TNF-inhibitor in ankylosing spondylitis: a population-based nationwide study. RMD Open. 2018;4(2):e000762. [DOI: 10.1136/rmdopen-2018-000762] [PMID: 30402269]
20. Shimabuco AY, Gonçalves CR, Moraes JCB, Waisberg MG, Ribeiro ACM, Sampaio-Barros PD, et al. Factors associated with ASDAS remission in a long-term study of ankylosing spondylitis patients under tumor necrosis factor inhibitors. Adv Rheumatol. 2018;58(1):40. [DOI: 10.1186/s42358-018-0040-x] [PMID: 30657103]
21. Vastesaeger N, Cruyssen BV, Mulero J, Gratacós Masmitjá J, Zarco P, Almodovar R, et al. REGISPONSER Working Group. ASDAS high disease activity versus BASDAI elevation in patients with ankylosing spondylitis as selection criterion for anti-TNF therapy. Reumatol Clin. 2014;10(4):204–9. [DOI: 10.1016/j.reuma.2013.12.006] [PMID: 24598027]

Постојаност терапије анти-ТНФ инхибиторима – подаци из Националног регистра за спондилоартритисе у Србији

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САЖЕТАК

Увод/Циљ Циљ истраживања је био да се ретроспективно анализирају подаци о ефикасности и постојаности терапије анти-ТНФα лековима код болесника са спондилоартритисом (СпА).

Методе Ретроспективно смо анализирали податке болесника са СпА уписаних у Српски национални регистар СпА. Сви болесници су подељени у две групе: они који су лечени једним анти-ТНФα леком и они који су преведени са првог на други и/или трећи анти-ТНФα лек. Активност болести је мерена скоровима *ASDAS* и *BASDAI*, а функционални статус је мерен скором *BASFI*.

Резултати Укључено је 290 болесника – 250 болесника са аксијалним СпА (ахСпА) и 40 са периферним СпА (пСпА). Од 250 болесника са аксСпА, 192 (76,8%) није променило први анти-ТНФα, док је 58 (23,2%) преведено на други, а 14 (5,6%) на трећи анти-ТНФ. Од 40 болесника са пСпА њих 29 (72,5%) остало је на првом анти-ТНФα, док је 11 (27,5%) преведено на други и три (7,5%) на трећи анти-ТНФα. Трајање лечења првим анти-ТНФα леком било је у просеку 35,16 ± 28,5 месеци (код оних који су мењали лек 29,41 ± 21,89 наспрам оних који нису 36,89 ± 30,04). У тренутку овог пресека 37 (19,3%) болесника је и даље имало веома високу активност болести, док је само 75 (39%) болесника имало неактивну болест.

Закључак У клиничкој пракси у нашој земљи, као и у другим земљама, постоји неспремност за прелазак са првог на други или трећи анти-ТНФα лек код болесника са СпА. Административна ограничења и ограничења Републичког фонда за здравствено осигурање могу бити један од главних разлога који отежавају лечење ових болесника. Поред тога, специфична ефикасност ових лекова на одређене ванзглобне манифестације болести често је разлог за избор лека прве линије или прелазак на други односно трећи лек.

Кључне речи: анти-ТНФα лекови; трајање лечења; регистар; спондилоартритис